Aortic Diameter Growth in Children With a Bicuspid Aortic Valve

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Knowledge of aortic growth in patients with bicuspid aortic valve (BAV) is essential to identify patients at risk for dissection, but data on children remain unclear. We retrospectively evaluated the aortic diameters of all pediatric BAV patients, identified through an echocardiographic database (2005 to 2013). Medical records were reviewed and aortic diameters re-measured on echocardiographic images at diagnosis and if available on variable mid- and endpoints follow-up. Dilatation (z-score >2) was based on 2 different z-score equation methods (Gautier/Campens). In 234 of the total 250 BAV patients, aortic diameters were analyzed; median age was 6.1 years (interquartile range 1.7 to 10), of which 63% were male. Aortic coarctation was present in 81 (36%) patients, 23% had a ventricular septal defect. BAV morphology according to Sievers was as follows: type 0 in 128 patients (55%), type 1 in 96 (41%), and type 2 in 10 (4%). Ascending aortic (AA) dilatation was present in 24% (Gautier) and 36% (Campens) at inclusion. Median follow-up was 4.7 years. The AA was the only location where mean z-scores progressed significantly with age: 0.06 (Gautier) and 0.09 (Campens) units per year between ages 5 and 15 years. Associations for higher AA z-scores at older age were an initial z-score >2 ($p < 0.001$) and aortic valve stenosis ($p < 0.05$). Neither dissection nor preventive aortic surgery occurred. In conclusion, only the AA seems at risk for complication, although no aortic complications occurred in this pediatric BAV cohort. BAV morphology seems associated with larger AA z-scores and valvular dysfunction. **(Am J Cardiol 2017;120:131−136)**

Bicuspid aortic valve (BAV) is the most common congenital heart defect and has considerable morbidity and mortality.[1−3] It occurs isolated or in combination with additional heart defects and may occur in the context of a syndrome.[1,4−7] In young adults, valve dysfunction requiring an intervention occurs frequently and valve dysfunction degree seems associated to BAV morphologic phenotype.[1,4,5,8−11] Aortic dilatation, predisposing for life-threatening rupture and dissection, is found in half of adult patients.[1,12−14] Dilatation rates and its associations are well studied in adults,[12,13,15,16] but for children these data are largely unclear.[8,10,17−19] In children, the aortic diameter is typically corrected, mostly for body size area, age, and gender. The advised method is to use z-scores (the number of standard deviations above or below the expected diameter). Different regression equations for expected aortic diameter and corresponding z-scores are currently in use, none of which having emerged as optimal. In the present study, we retrospectively investigated aortic diameter (z-score) change during follow-up and its possible associations in a pediatric cohort with BAV.

Methods

We included all children <18 years diagnosed with a BAV, who underwent echocardiography between 2005 and 2013 in our center. Echocardiographic studies were performed by trained sonographers using GE Vivid 7, E9, or S6 and assessed in EchoPac PC 113 (GE Healthcare). Correct diagnosis and BAV morphology were determined by 2 independent researchers (EV, MS) in parasternal short-axis view. In 25 inconclusive cases, a third experienced cardiologist (ALD) had decisive judgment. Aortic diameters were measured if at least 1 echocardiographic study, accompanied by height and weight data, provided good view of the ascending aorta (AA) distal to the sinotubular junction (STJ). Exclusion criterion was valve replacement before start of the study.

We reviewed medical records for cardiac anomalies, syndromes, interventions, and valve dysfunction at included echocardiographies. Lesions presented together as Shone's syndrome were scored separately for this study. Valve morphology was classified by the number of raphes

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Ethical approval: The Institutional Ethical Board (CMO Arnhem-Nijmegen) approved this study (ID 2015-1650) and concluded that no informed consent was needed as the treating doctors performed the study and the institution adopted an opt-out policy on scientific medical file research. All data were handled carefully and confidentially.

Reporting guidelines: The STROBE guidelines were followed.

See page 135 for disclosure information.

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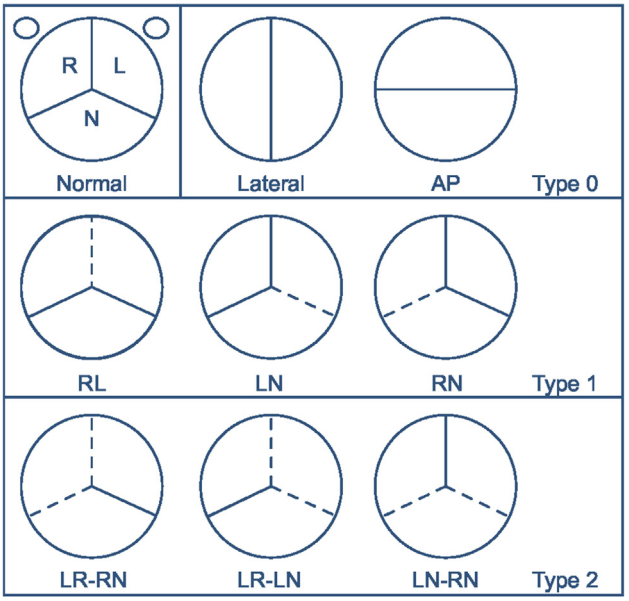

Figure 1. Sievers classification applied on echocardiography *(top view)*. "Type" represents the number of raphes, the subtype represents the spatial arrangement. AP = anteroposterior orientation; L = left coronary cusp; N = noncoronary cusp; R = right coronary cusp.

(malformed commissures) and spatial configuration of the cusps according to a pathological classification by Sievers and Schmidtke,[20] modified for echocardiography (Figure 1). Aortic valve stenosis (AS) was defined as a peak velocity (V_{max}) >2.5 m/s, as jet velocity is the strongest predictor for clinical outcome.[21] Aortic valve regurgitation was present when reported mild or more, based on jet evaluation and descending aortic backflow on color Doppler, left ventricular dimensions, and pressure half-time.[22] Patients were scored as having hypertension when they were medically treated for high blood pressure.

One researcher (RM) measured aortic diameters at the sinus of valsalva (SOV), STJ, and AA, defined as maximal diameter between STJ and aortic arch. Up to 3 studies were included (oldest, latest, and middlemost; ≥6 months apart). Measurements were performed in parasternal long-axis view at end-diastole, leading edge to leading edge, and perpendicular to the long axis of the aorta (Supplementary Figure 1).[23] Averages of 3 measurements, preferably in various cardiac cycles, were used. Missing height and weight data were interpolated if growth curves looked stable and had at least 4 points within 9 months.

Continuous variables are presented as mean (±SD) or median (interquartile range [IQR]) where appropriate, and categorical variables as frequencies. Differences were detected with Student's *t*, one-way analysis of variance, Pearson chi-square, Fisher's exact, or McNemar tests. Intraclass correlation and Bland-Altman plots assessed interobserver agreement on aortic measurements between 2 observers in 20 random patients. Aortic diameters were converted to z-scores using 2 different methods: by Gautier et al and by Campens et al. Both used the body surface area formula by Du Bois and both did not include neonates and toddlers,[24,25] although, as representative data on these very young children are lacking, we nevertheless chose to apply these methods. For this reason, we also performed additional regression analysis on absolute diameters at first examination. A z-score >2 was considered abnormal. Only Gautier's method was used for analysis of aortic growth in various subgroups. To account for dependency of serial measurements, the mean z-score over time was described with 5th order polynomials (quintics) constructed from a linear mixed-effects model, allowing single and serial measurements, unequal intervals, and a random intercept per subject. A likelihood ratio test assessed differences between subgroups. This model only allowed a univariate approach. p-values <0.05 were considered statistically significant. Analyses were performed in SPSS 20 (IBM Corp.).

Results

Of 11,792 children who underwent echocardiography, BAV was reported in 286. A total of 36 patients were excluded from the study because of incorrect diagnosis (n = 32), missing images (n = 1) or cardiac surgery distorting original valve anatomy before 2005 (n = 3). Of the 250 (2.1%) remaining patients, aortic diameters could be assessed in 234 (Ross procedure after 2005, n = 1; image storage errors, n = 4; inadequate images, n = 7; no height or weight data, n = 4), providing 580 studies. Table 1 describes their baseline characteristics, categorized by valve morphology. Median age at first valve intervention was 0.4 years (IQR 0 to 2.3). Patients with aortic coarctation had significantly lower rates of valve interventions compared with those without (7% vs 19%, p <0.05).

Interobserver agreement coefficients on aortic measurements were 0.98 (SOV), 0.87 (STJ), and 0.96 (AA). Overall difference between observers was −0.39 mm (p <0.01; Supplementary Figures 2 and 3). In 195 subjects, serial echocardiographic studies were available, with a median follow-up of 4.7 years (IQR 2.7 to 6.57). All ages were represented, with a slight overrepresentation of infants (Supplementary Figure 4). The median age at first examination was 6.1 years (IQR 1.7 to 10). During follow-up, 2 patients deceased (noncardiac death: 1 of hematologic and 1 of severe embryological disease) and 3 others underwent a Ross procedure for valve dysfunction, whereupon follow-up ended.

No aortic rupture, dissection, or preventive surgery was reported during follow-up. Mean z-scores and the prevalence of a z-score >2 at first examination were highest for the AA (Table 2), irrespective of the used z-score equation.[24,25] Figure 2 presents the 5th order polynomials best estimating the mean course of z-scores, with 95% confidence intervals of the estimate. The AA showed highest z-scores and was the only location demonstrating significant growth between ages 5 and 15 years, for both z-score equations: 0.67 to 1.24 (Gautier) and 0.45 to 1.29 (Campens), resulting in mean growth rates of 0.06 and 0.09 z-score units per year, respectively. Both methods showed no z-score progression for the SOV. The STJ was significantly greater than normal, but also nonprogressive. Significant differences are observed between both methods of z-score equation, particularly in the neonatal and toddler ages, with exceedingly high z-scores for Campens' equation.

Table 1
Demographics, categorized by Sievers' valve morphology

Characteristics	Total n = 234	Type 0		Type 1		Type 2
		AP	LAT	RL	RN	LR:RN
		n = 97 (42%)	n = 31 (13%)	n = 53 (23%)	n = 43 (18%)	n = 10 (4%)
Growth parameters (mean ± SD)						
Age (years)	6.4 ± 5.0	6.2 ± 5.5	6.9 ± 5.4	6.4 ± 4.9	6.2 ± 4.2	6.8 ± 3.1
Body Surface Area (m^2)	0.8 ± 0.4	0.8 ± 0.5	0.9 ± 0.5	0.8 ± 0.4	0.8 ± 0.4	0.9 ± 0.2
Body Mass Index (kg/m^2)	16 ± 3	16 ± 3	16 ± 3	16 ± 3	16 ± 2	15 ± 2
Male sex	63%	59%	52%	70%	65%	100%
Syndrome	11%	14%	7%	13%	7%	0%
Turner	5% †	5%	7%	8%	2%	0%
22q11 deletion	3%	5%	0%	2%	0%	0%
Other ‡	3%	4%	0%	4%	5%	0%
Cardiac malformations §						
Any**	57%	78%	35%	49%	35%	60%
Coarctation of the aorta**	36%	52%	16%	34%	14%	40%
Ventricular septal defect*	23%	33%	19%	19%	7%	30%
Patent ductus arteriosus	15%	23%	7%	9%	9%	10%
Atrial septal defect	9%	12%	7%	8%	9%	0%
Hypoplastic aortic arch	9%	12%	10%	4%	2%	20%
Other* ‡	33%	44%	19%	26%	23%	30%
Systemic hypertension ‖	5%	5%	7%	8%	0%	0%
Aortic valve dysfunction ‖						
Any**	57%	37%	74%	55%	81%	100%
Aortic valve stenosis**	40%	15%	61%	34%	72%	100%
Aortic valve regurgitation**	48%	30%	61%	47%	74%	70%
Aortic valve intervention**	16%	6%	23%	15%	35%	10%
2^{nd}	5%	.	.	.	.	.
3^{rd}, 4^{th}, 5^{th}	0.4%	.	.	.	.	.
Ascending aortic intervention	0%	.	.	.	.	.
Aortic arch intervention**	33%	50%	13%	30%	14%	40%

Significance of association between presented characteristic and BAV morphologic phenotype: *p <0.05, **p <0.001.
AP = anterior-posterior orientation; LAT = lateral orientation; RL = right-left coronary cusp fusion; RN = right-noncoronary cusp fusion; LR:RN = left-right and right-noncoronary cusp fusion.
† 13% of female subjects.
‡ Specification in Supplementary Table 1.
§ One patient can have several malformations.
‖ Considered present if seen in at least one of the echocardiographic studies.

Figure 3 shows a regression analysis of the absolute AA diameters at first examination of all patients and of 11 patients with isolated and, during follow-up, normally functioning BAV, including a correction for body surface area. Absolute AA diameter growth was 1.04 mm/year. We did not observe clinically relevant differences in subjects with aortic coarctation or valve dysfunction.

Figure 4 shows that an AA z-score >2 at inclusion was associated with a higher AA z-score at older age, compared with patients with an initial z-score <2 (p <0.001). However, the z-score progression rate ($\Delta z/\Delta t$) was only minimally different between both groups and thus larger AA diameter was not associated with *"faster"* AA growth. Presence of AS also resulted in significantly higher AA z-scores (p <0.05), but was associated to type 2 valve morphology (Table 1). However, the latter was present in only 10 patients. The presence of an initial z-score >2 was not associated to the presence of AS. Comparing patients with versus without aortic regurgitation, aortic arch and valve interventions, and specifically a history of coarctation did not result in significant differences in estimated z-score course.

For the SOV, a z-score >2 at inclusion (p <0.001), male gender (p <0.01), Sievers' type 2 (p <0.01), syndromes (p <0.001), and absence of AS (p <0.05) were associated with higher z-scores (Supplementary Figure 5). However, these factors were not independent: subjects with a syndrome more often had an initial z-score >2 (23% vs 6%, p <0.05) and less often had AS (28% vs 60%, p <0.01). Subjects with AS less often had an initial z-score >2 (4% vs 13%, p <0.05). Higher STJ z-scores were observed in syndromes (p <0.05), subjects with an initial z-score >2 (p <0.001), and right-non coronary cusp fusion subtype within Sievers' type 1 valve morphology (p <0.01; Supplementary Figure 6), but again, they were nonprogressive.

Discussion

In this large population of children with BAV, we observed no rupture, dissection, or need for preventive aortic surgery. Only the AA z-score progressed with time, showing that the main emphasis on follow-up should lie on the aortic diameters at this location. An initial z-score >2

Table 2
Mean z-scores and prevalence of a z-score >2 at first echocardiography (n = 234, median age = 6.1 years)

	Gautier's equation	Campens' equation	p-value
Z-score (mean ±SD)			
Sinus of Valsalva	-0.2 ± 1.5	0.6 ± 1.5 ‡	<0.001
Sinotubular junction	0.3 ± 1.8 †	-	-
Ascending aorta	0.8 ± 1.7 ‡	1.4 ± 2.2 ‡	<0.001
Z-score >2 (% ±SE)			
Sinus of Valsalva	8 ± 2	15 ± 2	<0.001*
Sinotubular junction	15 ± 2	-	-
Ascending aorta	24 ± 3	36 ± 3	<0.001*

Significance compared with normal population (mean z-score = 0): †p <0.01; ‡p <0.001.
Campens did not provide an equation for the sinotubular junction.
* McNemar test.

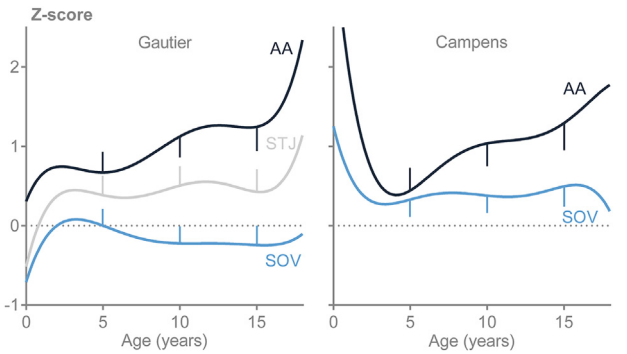

Figure 2. Estimated mean z-scores plotted as a quintic function against age, based on 2 methods of z-score equation. Error bars denote half 95% confidence intervals of the estimate. Functions are displayed in Supplementary Table 2, for reproducibility reasons. AA = ascending aorta; SOV = sinus of Valsalva; STJ = sinotubular junction.

and presence of AS were clinical markers for higher z-scores in early adulthood, but z-score progression was not *faster*. Indeed, aortic pathology in the context of BAV seems not a clinical problem in childhood. Previous studies compared contributing factors using numerical growth rates. This is the first study providing a visualized comparison of aortic diameter growth in children with a BAV.[8,10,17−19]

As expected, BAV was common in our pediatric cardiology department and clearly associated with valve- and non−valve-related morbidity such as coarctation of the aorta,[2,26] but also with other anomalies such as ventricular septal defects and patent ductus arteriosus, for which only putative associations were mentioned.[5−7,27−29] Awareness and echocardiographic screening for other anomalies in clinical practice is mandatory. Similar to Fernandes et al,[9] valve interventions occurred in a minority and mainly early in life, typically for aortic stenosis. Most importantly, no intervention for aortic dilatation was needed and no complications of aortic dilatation occurred. However, some follow-up seems warranted as we do not want to miss the individual patient with rapid increase in diameter. For the patient with isolated, normally functioning BAV, we suggest to perform echocardiography every 5−10 years.

The AA shows the largest relative diameter and clearly grows faster than can be expected based on body growth and/or age. No significant differences in absolute AA diameter were observed between patients with isolated BAV and BAV patients with associated lesions or valve dysfunction. However, the isolated BAV group was only small. Although patients with an initial z-score >2 and patients with AS had a higher initial z-score, they all had similar AA growth, which makes AA diameter growth predictable. The progression of 0.06 to 0.09 z-score units per year was notably similar to literature that likewise used z-scores,[8,10] as was absolute aortic diameter growth.[17] Fernandes et al[8] earlier concluded that young patients initially presenting with higher z-scores seem to be at highest risk for aortic dilatation at later age, and this seems valid for all locations. It seems logical that only the AA is at risk for dilatation-related complications, as it is the only location showing z-score progression, but whether these patients indeed have an elevated need to undergo (preventive) aortic surgery at later age is not well studied. We propose regular follow-up for patients entering young adulthood to overcome this gap in knowledge.

Earlier studies suggested protective effects of a coarctation history on AA z-score progression, but we could not confirm this finding.[8,13,15] Also, aortic regurgitation and aortic or valvular interventions were not associated with aortic size. Previous studies reported conflicting data on the increase of aortic dimensions at the level of the SOV.[8,10,17−19] We found no z-score progression at this level. The clinical relevance of having an underlying syndrome on STJ diameters remains unclear, mainly because of the heterogeneity of this group.

It is suggested that in adult cohorts, BAV morphology is associated with valve dysfunction and complications.[3−6] Our study confirms this in a pediatric cohort. Valve morphology should be determined at young age, for which in our opinion Sievers' classification is applicable. Distribution of BAV morphology differed from Sievers' original study, possibly because of differences in age category.[20] Comparing studies that included BAV morphology is challenging because of a large variety in classifications. Many studies applied morphologic classification named after localization of 1 supposed fusion line (right-left, right-non and left-non coronary cusp fusion), whereas Sievers' classification also allows 0 and 2 fusion lines.[5,8,9] Given the visual similarities between type 0 anteroposterior orientation and type 1 right-left coronary cusp fusion and between type 0 lateral orientation and type 1 right-left or left-non coronary cusp fusion (Figure 1), distribution of morphology, valve dysfunction, and interventions were notably similar to the literature.[5,9]

z-score equation methods by Gautier et al and Campens et al regrettably are not designed for use in patients below 2 years, causing z-scores in these subjects to be only based on extrapolated data and difficult to interpret.[24,25] Both methods provide clearly different results in this age group, with Campens' method appearing the least accurate. For this reason, we calculated the annual z-score progression in children between 5 and 15 years. As we clinically found children presenting with AA z-scores >2 to have larger AAs in adolescence, we urge the need for z-score validation in

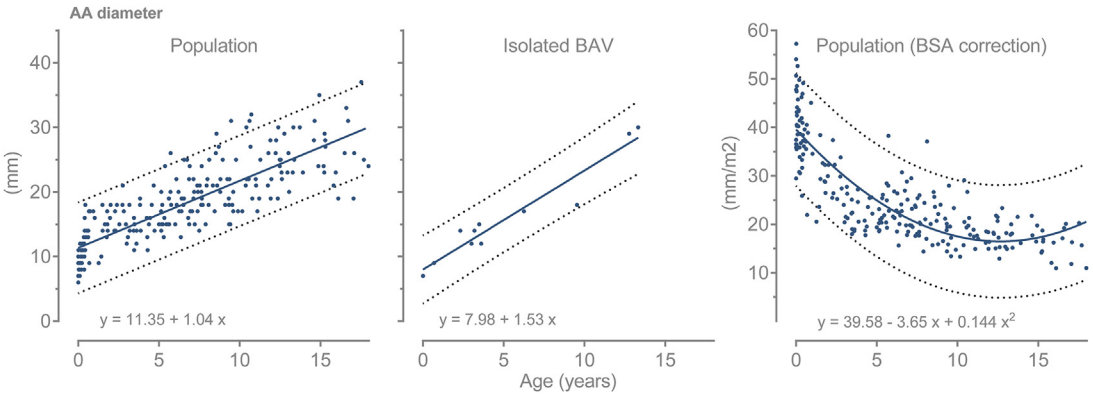

Figure 3. Regression analysis of absolute AA diameters in mm at first echocardiographic examination of all patients, including a correction for body surface area, and of 11 patients with isolated and, during follow-up, normal functioning BAV. Dotted lines denote 95% prediction intervals. AA = ascending aorta; BSA = body surface area.

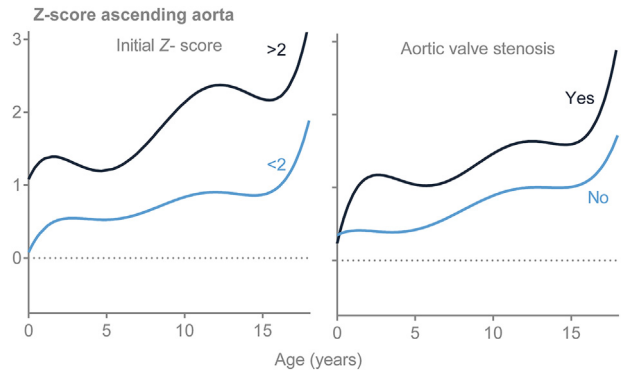

Figure 4. Ascending aortic z-scores plotted against age, broken down by their significant associations: z-score at first examination ($p < 0.001$) and aortic valve stenosis ($p < 0.05$).

cohorts with sufficient representation of neonates and toddlers, for the clinician to be aware of the expected growth. Instead of using the z-score, we propose to use Figure 3 to evaluate whether a specific AA diameter is abnormal for a child with a BAV and possibly associated with complications later in life. This could be of benefit especially in patients younger than 5 years of age as the z-score has clear limitations here. Patients with an AA diameter above the 95% prediction interval of our BAV cohort should therefore probably be controlled more frequently.

All limitations of a retrospective study apply. We studied subjects in our tertiary center, introducing a selection bias. Two-dimensional echocardiography might not represent the 3-dimensional aortic shape and might have been subject to technical improvement during the study. We nonetheless believe in the reproducibility of this study with high inter-observer agreement and observed differences within reported measurement variability.[23] Echocardiography is still the primary investigation of choice for diagnosis and follow-up of children with a BAV, making our results applicable to most clinical situations. Our predictions lack external validation and we hope other research groups will provide this in the near future. The elementary shape of a 5th order polynomial might influence results in the extreme ages, although accuracy is suggested by the population size.

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.amjcard.2017.03.245.

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